FILE 'USPAT' ENTERED AT [redacted]43:09 ON 28 JAN 1999

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  *                  W E L C O M E   T O   T H E                *
  *          U. S.   P A T E N T   T E X T   F I L E            *
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=> e Blumberg, Richard/in

E#	FILE	FREQUENCY	TERM
E1	USPAT	2	BLUMBERG, REVITAL/IN
E2	USPAT	1	BLUMBERG, REX H/IN
E3	USPAT	0 -->	BLUMBERG, RICHARD/IN
E4	USPAT	1	BLUMBERG, RICHARD A/IN
E5	USPAT	2	BLUMBERG, RICHARD J/IN
E6	USPAT	1	BLUMBERG, RICHARD JAY/IN
E7	USPAT	3	BLUMBERG, RUTH/IN
E8	USPAT	1	BLUMBERG, SHLOMO/IN
E9	USPAT	7	BLUMBERG, SHMARYAHU/IN
E10	USPAT	1	BLUMBERG, SHMARYAHUM/IN
E11	USPAT	1	BLUMBERG, SIDNEY/IN
E12	USPAT	4	BLUMBERG, STANLEY/IN

=> s (antibod? or IgG) and oral? deliver?/clm

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         33273 ANTIBOD?
         11686 IGG
         11316 ORAL?/CLM
         79998 DELIVER?/CLM
            60 ORAL? DELIVER?/CLM
                 ((ORAL?(W)DELIVER?)/CLM)
L1           18 (ANTIBOD? OR IGG) AND ORAL? DELIVER?/CLM
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=> t l1 1-18

1. 5,840,342, Nov. 24, 1998, Shark liver extract for stimulating the immune system; Lawrence R. Raithaus, 424/553, 520 [IMAGE AVAILABLE]

2. 5,840,318, Nov. 24, 1998, Methods and compositions for modulating immune systems of animals; William E. Marshall, et al., 424/282.1, 93.1, 93.4, 93.42, 93.45, 93.46, 93.48, 115, 278.1, 433, 434, 464 [IMAGE AVAILABLE]

3. 5,830,898, Nov. 3, 1998, Enantiomerically pure .beta.-di-dioxolane-nucleosides with selective anti-hepatitis B virus activity; Raymond F. Schinazi, 514/262, 266; 544/277 [IMAGE AVAILABLE]

4. 5,817,624, Oct. 6, 1998, Permeation enhancer compositions for increased absorption of therapeutic proteins through the colonic membrane; Heechung Yang, et al., 514/3, 12, 730, 806 [IMAGE AVAILABLE]

5. 5,811,388, Sep. 22, 1998, Delivery of drugs to the lower GI tract; David R. Friend, et al., 514/2; 424/85.1, 465, 474, 475, 479, 481, 485, 488; 514/3, 12, 21, 177, 178, 179, 180, 181, 182, 777, 780, 782, 960, 961 [IMAGE AVAILABLE]

6. 5,807,832, Sep. 15, 1998, Oral delivery of biologically active substances bound to vitamin B.sub.12; Gregory John Russell-Jones, et al., 514/21; 424/193.1, 194.1; 514/2, 12, 15, 52 [IMAGE AVAILABLE]

7. 5,795,859, Aug. 18, 1998, Peptide which abrogates TNF and/or LPS toxicity; Deborah A. Rath[illegible]n, et al., 514/12; 424/185.1; 530/324 [IMAGE AVAILABLE]

8. 5,792,451, Aug. 11, 1998, Oral drug delivery compositions and methods; Donald J. Sarubbi, et al., 424/85.4, 85.2, 141.1, 184.1, 465, 474, 489, 491, 499; 514/2, 12, 21, 773 [IMAGE AVAILABLE]

9. 5,762,904, Jun. 9, 1998, Oral delivery of vaccines using polymerized liposomes; Junichi Okada, et al., 424/1.21; 264/4.1, 4.3; 424/9.321, 9.4, 9.51, 9.6, 184.1, 278.1, 450, 812; 428/402.2 [IMAGE AVAILABLE]

10. 5,656,294, Aug. 12, 1997, Colonic delivery of drugs; David R. Friend, et al., 424/465, 485, 488; 514/177, 178, 179, 180, 181, 182, 777, 780, 782 [IMAGE AVAILABLE]

11. 5,589,463, Dec. 31, 1996, Oral delivery of biologically active substances bound to vitamin B12; Gregory J. Russell-Jones, et al., 514/21; 424/194.1; 514/12, 52; 530/405; 536/26.4, 26.41, 26.44 [IMAGE AVAILABLE]

12. 5,587,362, Dec. 24, 1996, L-nucleosides; Chung K. Chu, et al., 514/46; 424/420, 457; 514/47, 49, 50, 51; 536/26.26, 26.7, 26.8, 27.6, 28.5, 28.54, 28.55 [IMAGE AVAILABLE]

13. 5,523,290, Jun. 4, 1996, Antiproliferation factor; Robert D. LeBoeuf, et al., 514/21; 424/85.1; 514/12; 530/350, 351, 387.1, 388.7, 388.73, 388.75, 388.8, 389.6, 389.7, 395, 854 [IMAGE AVAILABLE]

14. 5,451,411, Sep. 19, 1995, Methods and compositions for the oral delivery of therapeutic agents; Wayne R. Gombotz, et al., 424/499, 400 [IMAGE AVAILABLE]

15. 5,444,063, Aug. 22, 1995, Enantiomerically pure .beta.-D-dioxolane nucleosides with selective anti-Hepatitis B virus activity; Raymond F. Schinazi, 514/262, 266 [IMAGE AVAILABLE]

16. 5,428,023, Jun. 27, 1995, Oral delivery of biologically active substances bound to vitamin B12 or analogues thereof; Gregory J. Russell-Jones, et al., 514/21; 424/85.4, 193.1, 194.1; 514/2, 4, 6, 12, 15, 52; 530/303, 306, 313, 345, 351, 398, 399, 405, 409; 536/26.4, 26.41, 26.44 [IMAGE AVAILABLE]

17. 5,422,097, Jun. 6, 1995, Combined antiviral and antimediator treatment of common colds; Jack M. Gwaltney, Jr., 424/45, 405, 408 [IMAGE AVAILABLE]

18. 5,162,037, Nov. 10, 1992, Magnetically influenced homeopathic pharmaceutical formulations, methods of their preparation and methods of their administration; Walter Whitson-Fischman, 600/12; 128/907; 600/15 [IMAGE AVAILABLE]

=> t 2, 5, 6 ti clm

US PAT NO: 5,840,318 [IMAGE AVAILABLE] L1: 2 of 18
TITLE: Methods and compositions for modulating immune systems of animals

CLAIMS:

CLMS(1)

What is claimed is:

1. A method for activating and modulating the immune system of an animal comprising:
(a) growing bacteria in a medium, wherein the bacteria is of a class selected from the group consisting of Lactobacillus, Staphylococcus, Streptococcus, Pseudomonas, Bacillus, Escherichia, Enterococcus, and Klebsiella;
(b) exposing said bacteria to biological, chemical or physical stress so that the bacteria release a stress release product into the medium;
(c) removing said bacteria from said medium and said stress release product to form a separated product;
(d) filtering said separated product through a filter having a 10,000 dalton molecular weight cutoff to obtain said stress release product; and
(e) administering an effective amount of said stress release product to said animal.

CLMS(2)

2. The method of claim 1 wherein the step of stressing said bacteria is selected from the group consisting of:
altering the pH of said media to affect the bioavailability of nutrients in said media,
removing nutrients from said media,
crowding by reducing the volume of said media, adding additional bacterial to said media, and
removing said bacteria from said media by centrifugation and resuspending said bacteria in a non-nutritive isotonic solution.

CLMS(3)

3. The method of claim 1 wherein said non-nutritive isotonic solution comprises 0.9% sodium chloride.

CLMS(4)

4. The method of claim 2 wherein said non-nutritive isotonic solution is 0.1M phosphate buffer having a pH of 7.5.

CLMS(5)

5. A method for modulating the immune system of an animal comprising:
administering to said animal an effective amount of a product released by bacteria in response to stress wherein the stress release product is made by a method comprising:
(a) growing bacteria in a medium, wherein the bacteria is of a class selected from the group consisting of Lactobacillus, Staphylococcus, Streptococcus, Pseudomonas, Bacillus, Escherichia, Enterococcus, and Klebsiella;
(b) exposing said bacteria to biological, chemical or physical stress so that the bacteria release a stress release product into the medium;
(c) removing said bacteria from said medium and said stress release product to form a separated product;
(d) filtering said separated product through a filter having a 10,000 dalton molecular weight cutoff to obtain said stress release product; and
(e) administering an effective amount of said stress release product to said animal and further providing that the stress release product is administered to the animal in a delivery form selected from the group consisting of forms for parenteral delivery, gels for **oral** **delivery**, lozenges for **oral** **delivery**, nasal sprays, ear drops, vaginal creams, vaginal suppositories, and topical ointments.

CLMS(6)

6. The method of claim 5 wherein said animal is selected from the group consisting of humans, poultry and livestock.

CLMS(7)

7. The method of claim 5 wherein said stress release product is administered in a concentration of about 1000 to 50,000 AU of said stress release product/ml.

CLMS(8)

8. The method of claim 7 wherein said stress release product is administered orally or parenterally.

CLMS(9)

9. The method of claim 5 wherein the stress release product has a size of between 0.5 and 3 kDa.

CLMS(10)

10. The method of claim 5 wherein said stress release product is administered daily for five consecutive days.

CLMS(11)

11. The method of claim 5 wherein said stress release product is administered with a killed pathogen.

CLMS(12)

12. A method of maintaining the viability of bacteria during storage and shipment comprising:
administering to said bacteria a product released by bacteria in response to stress, wherein the stress release product is made by a method comprising:
(a) growing bacteria in a medium, wherein the bacteria is of a class selected from the group consisting of Lactobacillus, Staphylococcus, Streptococcus, Pseudomonas, Bacillus, Escherichia, Enterococcus, and Klebsiella;
(b) exposing said bacteria to biological, chemical or physical stress so that the bacteria release a stress release product into the medium;
(c) removing said bacteria from said medium and said stress release product to form a separated product; and
(d) filtering said separated product through a filter having a 10,000 dalton molecular weight cutoff to obtain said stress release product.

CLMS(13)

13. The method according to claim 1 wherein the bacteria is selected from the group consisting of L. acidophilus, L. caseii, L. fermentum, L. plantarum, L. monocytogenes, S. aureus, S. typhimurium, P. acidolactici, B. coryneforme, E. coli, E. faecium, S. pyogenes, and K. pneumoniae.

CLMS(14)

14. A method for activating and modulating the immune system of an animal comprising:
(a) growing bacteria in a medium, wherein the bacteria is selected from the group consisting of L. acidophilus, L. caseii, L. fermentum, L.

plantarum, L. monocytogenes, S. aureus, S. typhimurium, P. acidolactici, B. coryneform, E. coli, E faecium, S. pyogenes, and K. pneumoniae;
(b) exposing said bacteria to biological, chemical or physical stress such that the bacteria release a stress release product;
(c) removing said bacteria from said medium and said stress release product to form a separated product;
(d) filtering said separated product through a filter having a 10,000 dalton molecular weight cutoff to obtain said stress release product; and
(e) administering an effective amount of said stress release product to said animal.

US PAT NO: 5,811,388 [IMAGE AVAILABLE] L1: 5 of 18
TITLE: Delivery of drugs to the lower GI tract

CLAIMS:

CLMS(1)

What is claimed is:

1. A pharmaceutical tablet having an inner composition optionally coated by a pharmaceutically-acceptable coating, said tablet designed for **orally** **delivering** a therapeutically effective amount of a drug to the lower GI tract without significant release of the drug in the upper GI tract after oral administration of the tablet, which inner composition of the tablet comprises
about 0.01% by weight to about 10.0% by weight of a drug useful for treating a lower GI tract disorder;
about 40% by weight to about 98% by weight of a hydrocolloid gum obtainable from higher plants; and
about 2% by weight to about 50% by weight of a pharmaceutically acceptable excipient;
no enteric polymeric material or gas-forming excipient, wherein the components of the inner composition are distributed so that the drug is concentrated in an active core with the gum and excipient surrounding the active core.

CLMS(2)

2. The tablet of claim 1, wherein said tablet is designed for **orally** **delivering** a therapeutically effective amount of a drug to the colon.

CLMS(3)

3. The tablet of claim 1, which is enterically coated.

CLMS(4)

4. The tablet of claim 3, wherein the drug is a corticosteroid.

CLMS(5)

5. The tablet of claim 4, wherein the corticosteroid is present in an amount of about 1% by weight to about 4% by weight of the inner composition.

CLMS(6)

6. The tablet of claim 5, wherein the corticosteroid is dexamethasone, budesonide, fluticasone, prednisone, prednisolone or hydrocortisone.

CLMS(7)

7. The tablet of claim 6, wherein the corticosteroid is micronized budesonide.

CLMS(8)

8. The tablet of claim 6 wherein the corticosteroid is micronized dexamethasone.

CLMS(9)

9. The tablet of claim 1, wherein the drug is 5-ASA.

CLMS(10)

10. The tablet of claim 1, wherein the drug is a peptide.

CLMS(11)

11. The tablet of claim 10, wherein the peptide is LHRH, growth hormone, vasopressin, insulin, calcitonin, glucagon, GHRH, relaxin, somatostatin, a cytokine or a lymphokine.

CLMS(12)

12. The tablet of claim 1, wherein the drug is a stimulant laxative.

CLMS(13)

13. The tablet of claim 12, wherein the drug is a bisacodyl.

CLMS(14)

14. The tablet of claim 1, wherein the hydrocofloid is guar gum, locust bean gum, gum tragacanth or karaya gum.

CLMS(15)

15. The tablet of claim 14, wherein the hydrocofloid is guar gum.

CLMS(16)

16. A method for treating a disorder of the lower GI tract in a human subject, which method comprises orally-administering to a human subject in need thereof a tablet of claim 1.

CLMS(17)

17. The method of claim 16, wherein the inner composition comprises
about 0.5% by weight to about 5.0% by weight of a drug useful in treating a colonic disorder;
about 50% by weight to about 70% by weight of a hydrocolloid gum obtainable from higher plants;
about 25% by weight to about 50% by weight of the pharmaceutically-acceptable excipient.

CLMS(18)

18. The method of claim 16, wherein the disorder is characterized by inflammation of the colon and the drug is a corticosteroid.

CLMS(19)

19. The method of claim 16, wherein the corticosteroid is present in an amount of about 1% by weight to about 4% by weight.

CLMS(20)

20. The method of claim 19, wherein the corticosteroid is dexamethasone, budesonide, fluticasone, prednisone, prednisolone or hydrocortisone.

CLMS(21)

21. The method of claim 16, wherein the drug is 5-ASA.

CLMS(22)

22. The method of claim 16, wherein the hydrocolloid is guar gum, locust bean gum, gum tragacanth or karaya gum.

CLMS(23)

23. The method of claim 22, wherein the hydrocolloid is guar gum.

CLMS(24)

24. A method for preferentially delivering a drug to the lower GI tract wherein such drug is susceptible to enzymatic degradation in the upper GI tract, which method comprises orally-administering to a human subject in need thereof a tablet of claim 1.

CLMS(25)

25. The method of claim 24, wherein the drug is a peptide.

CLMS(26)

26. The method of claim 25, wherein the peptide is LHRH, growth hormone, vasopressin, insulin, calcitonin, glucagon, GHRH, relaxin, somatostatin, a cytokine or a lymphokine.

CLMS(27)

27. The method of claim 25, wherein the peptide is nafarelin, busarelin, goserelin, leuprolide, or a pharmaceutically-acceptable salt thereof and is delivered to treat endometriosis in a female human subject.

CLMS(28)

28. The method of claim 16, wherein the disorder is constipation and the drug is a stimulant laxative.

CLMS(29)

29. The method of claim 16, wherein the disorder is characterized by inflammation of the colon and the drug is 5-ASA.

CLMS(30)

30. The tablet of claim 10, wherein the peptide is selected from the group consisting of nafarelin, busarelin, goserelin, leuprolide, and a pharmaceutically-acceptable salt thereof.

US PAT NO: 5,807,832 [IMAGE AVAILABLE] L1: 6 of 18
TITLE: Oral delivery of biologically active substances bound to

CLAIMS:

CLMS(1)

We claim:

1. A method of treating a patient in need of treatment with a biologically active substance selected from the group consisting of a protein, a peptide, a hormone, and a polysaccharide, comprising the steps of

(1) providing an orally administrable complex comprising said biologically active substance covalently linked to a vitamin B12 carrier molecule, wherein said carrier molecule is capable of binding in vivo to intrinsic factor, thereby enabling uptake and transport of the complex from the intestinal lumen of said patient via intrinsic factor to the systemic circulation of said patient, and

(2) orally administering said complex to said patient so as to elicit a physiological effect associated with the presence of said biologically active substance in the systemic circulation of said patient.

CLMS(2)

2. The method according to claim 1, wherein said biologically active substance is a hormone selected from the group consisting of luteinizing hormone releasing hormone, insulin, testosterone, pregnant mare serum gonadotrophin, human chorionic gonadotrophin and inhibin.

CLMS(3)

3. The method according to claim 2, wherein said hormone is the lys-6 form of LHRH.

CLMS(4)

4. The method according to claim 1, wherein said biologically active substance is a protein, peptide, or polysaccharide antigen or hapten, wherein said antigen or hapten is selected from the group consisting of grass pollen, weed pollen, tree pollen, plant pollen, cat hair, dog hair, pig hair, or other epithelia, house dust mite, wheat chaff, and kapok antigens or haptens, or

wherein said antigen or hapten is selected from the group consisting of a protein from or immunogens against influenza, measles, Rubella, smallpox, yellow fever, diphtheria, tetanus, cholera, plague, typhus, BCG, tuberculosis causing agents, Haemophilus influenza, Neisseria catarrhalis, Klebsiella pneumoniae, pneumococci, streptococci, a malarial parasite and a causative agent of coccidiosis in chickens, or wherein said antigen or hapten is a secretory product from an organism selected from the group consisting of diphtheria, tetanus, cholera, plague, typhus, and tuberculosis causing agents, Haemophilus influenza, Neisseria catarrhalis, Klebsiella pneumoniae, pneumococci, and streptococcus mutans.

CLMS(5)

5. A method of treating a patient in need of treatment with a biologically active substance, comprising the steps of

(1) providing an orally administrable complex comprising said biologically active substance covalently linked to a vitamin B12 carrier molecule, wherein said carrier molecule is capable of binding in vivo to intrinsic factor, thereby enabling uptake and transport of the complex from the intestinal lumen of said patient via intrinsic

factor to the systemic circulation of said patient, and
(2) orally administering said complex to said patient so as to elicit a physiological effect associated with the presence of said biologically active substance in the systemic circulation of said patient, wherein said biologically active substance is a therapeutic agent selected from the group consisting of neomycin, salbutamol, pyrimethamine, penicillin G, methicillin, carbenicillin, pethidine, xylazine, ketamine hydrochloride, mephenesin and iron dextran.

CLMS(6)

6. The method according to claim 1, wherein said vitamin B12 carrier molecule is selected from the group consisting of cyanocobalamin, aquocobalamin, adenosylcobalamin, methylcobalamin, hydroxycobalamin, cyanocobalamin carbanilide, 5-0-methylbenzylcobalamin, desdimethyl, monoethylamide and methylamide analogues of cyanocobalamin, aquocobalamin, adenosylcobalamin, methylcobalamin, hydroxycobalamin, cyanocobalamin carbanilide and 5-0-methylbenzylcobalamin, coenzyme B12, 5'-deoxyadenosyl-cobalamin, chlorocobalamin, sulphitocobalamin, nitrocobalamin, thiocyanatocobalamin, adenosylcyanocobalamin, cobalamin lactone, cobalamin lactam, vitamin B12 anilide, vitamin B12 propionamide, and a vitamin B12 molecule in which one or two corrin ring side chains are free carboxylic acids.

CLMS(7)

7. The method according to claim 1, wherein said vitamin B12 carrier molecule includes a central metal atom selected from the group consisting of Ni and Zn.

CLMS(8)

8. The method according to claim 1, wherein said vitamin B12 carrier molecule is a cyanocobalamin methylamide or a cobalamin ethylamide.

CLMS(9)

9. The method according to claim 1, wherein said vitamin B12 carrier molecule is selected from the group consisting of 5,6-dichlorobenzimidazolecobalamin, 5-hydroxybenzimidazole-cobalamin, and trimethylbenzimidazolecobalamin.

CLMS(10)

10. The method according to claim 1, wherein said biologically active substance is covalently linked via a cross-linking agent to a vitamin B12 carrier molecule and said cross-linking agent is selected from the group consisting of a N-(4-azidophenylthio)phthalimide, 4,4'-dithiobis-phenylazide, dithiobis(succinimidylpropionate), dimethyl-3,3'-dithiobispropionimidate.2HCl, 3, 3 '-dithiobis(sulphosuccinimidyl-propionate), ethyl-4-azidophenyl-1, 4-dithiobutyrimidate.HCl, N-succinimidyl-(4-azidophenyl)-1,3'-dithiopropionate, sulphosuccinimidyl-2-(p-azidosalicylamido)-ethyl-1,3'-dithiopropionate, N-succinimidyl-3-(2-pyridyldithio)propionate, sulphosuccinimidyl-(4-azidophenyldithio)-propionate and 2-iminothiolane.

CLMS(11)

11. The method according to claim 10, wherein said cross-linking agent is bis(2-(succinimidyloxycarbonyloxy)-ethyl)sulphone.

CLMS(12)

12. The method according to claim 1 wherein said biologically active substance is administered orally in a formulation comprising
(i) an orally administrable complex comprising said biologically active substance covalently linked via a cross-linking agent to a vitamin B12 carrier molecule, wherein
(A) said carrier molecule is capable of binding in vivo to intrinsic factor, thereby enabling uptake and transport of the complex from the intestinal lumen of said patient via intrinsic factor to the systemic circulation of said patient, and
(B) said cross-linking agent links said biologically active substance to a carboxyl group of an acid-hydrolyzed propionamide side chain adjacent to ring A, ring B or ring C of said carrier molecule;
and
(ii) an orally and pharmaceutically acceptable carrier or diluent.

CLMS(13)

13. The method according to claim 12, wherein said formulation is in an **oral** **delivery** form selected from the group consisting of a capsule, a tablet, an emulsion, a viscous colloidal dispersion, an elixir, a gel and a paste.

=> s (antibod?/clm or IgG/clm) and oral?

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          8937 ANTIBOD?/CLM
           821 IGG/CLM
         74056 ORAL?
L2        1403 (ANTIBOD?/CLM OR IGG/CLM) AND ORAL?
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=> s l2 and (administr?/clm or deliver?/clm)

```
         12159 ADMINISTR?/CLM
         79998 DELIVER?/CLM
L3         250 L2 AND (ADMINISTR?/CLM OR DELIVER?/CLM)
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=> s l3 and antibod? conjugat?

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         33273 ANTIBOD?
         51642 CONJUGAT?
          2722 ANTIBOD? CONJUGAT?
                 (ANTIBOD?(W)CONJUGAT?)
L4          24 L3 AND ANTIBOD? CONJUGAT?
```

=> t l4 1-24

1. 5,851,829, Dec. 22, 1998, Method of intracellular binding of target molecules; Wayne A. Marasco, et al., 435/328; 424/577, 578; 435/325, 326, 330, 333, 339, 339.1, 366, 372, 419 [IMAGE AVAILABLE]

2. 5,846,537, Dec. 8, 1998, Modified avidin and streptavidin and methods of use thereof; Scott F. Rosebrough, 424/178.1, 1.49, 9.1, 9.34, 9.35, 179.1, 183.1; 530/395, 402, 403, 406 [IMAGE AVAILABLE]

3. 5,843,913, Dec. 1, 1998, Nucleic acid respiratory syncytial virus vaccines; Xiaomao Li, et al., 514/44; 435/91.4, 320.1 [IMAGE AVAILABLE]

4. 5,843,397, Dec. 1, 1998, Cytotoxic therapy for graft rejection; Milton David Goldenberg, 424/1.41, 1.11, 9.1 [IMAGE AVAILABLE]

5. 5,827,534, Oct. 27, 1998, **Oral** dosage composition comprising zonnula occludens toxin and a therapeutic agent for intestinal delivery; Alessio Fasano, 424/451, 130.1, 184.1, 236.1, 464, 800, 804, 806; 514/2,

3, 837, 866 [IMAGE AVAILABLE]

6. 5,817,631, Oct. 6, 19[redacted], Therapeutic uses of mela[redacted]n; David L. Berliner, et al., 514/21; 424/94.4, 195.11; 514/64, 567 [IMAGE AVAILABLE]

7. 5,773,435, Jun. 30, 1998, Prodrugs for .beta.-lactamase and uses thereof; John Kadow, et al., 514/214; 540/222, 225, 226 [IMAGE AVAILABLE]

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9. 5,736,139, Apr. 7, 1998, Treatment of Clostridium difficile induced disease; John A. Kink, et al., 424/164.1, 167.1; 530/389.1, 389.5 [IMAGE AVAILABLE]

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11. 5,677,174, Oct. 14, 1997, Isolated porcine pancreatic cells for use in treatment of diseases characterized by insufficient insulin activity; Jonathan Dinsmore, 435/325 [IMAGE AVAILABLE]

12. 5,665,353, Sep. 9, 1997, Composition containing an analog of haemophilus Hin47 with reduced protease activity; Sheena M. Loosmore, et al., 424/94.63, 94.64; 435/220; 514/2, 12 [IMAGE AVAILABLE]

13. 5,660,829, Aug. 26, 1997, Process for antibody directed enzyme prodrug therapy; Philip John Burke, et al., 424/178.1, 182.1; 514/476; 560/134, 135, 136, 137 [IMAGE AVAILABLE]

14. 5,609,846, Mar. 11, 1997, Radiolabelled antibody cytotoxic therapy of infectious or autoimmune disease; Milton D. Goldenberg, 424/1.41, 1.49, 85.2 [IMAGE AVAILABLE]

15. 5,595,721, Jan. 21, 1997, Radioimmunotherapy of lymphoma using anti-CD20; Mark S. Kaminski, et al., 424/1.49, 144.1 [IMAGE AVAILABLE]

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17. 5,527,527, Jun. 18, 1996, Transferrin receptor specific antibody-neuropharmaceutical agent conjugates; Phillip M. Friden, 424/178.1; 530/391.1, 391.7, 399 [IMAGE AVAILABLE]

18. 5,332,567, Jul. 26, 1994, Detection and treatment of infections with immunoconjugates; M. David Goldenberg, 424/1.49, 1.53, 9.341, 136.1, 159.1, 164.1, 178.1 [IMAGE AVAILABLE]

19. 5,182,107, Jan. 26, 1993, Transferrin receptor specific antibody-neuropharmaceutical or diagnostic agent conjugates; Phillip M. Friden, 424/179.1, 94.1, 143.1, 178.1; 514/21; 530/387.3, 388.22, 391.1, 391.7, 391.9, 399 [IMAGE AVAILABLE]

20. 5,154,924, Oct. 13, 1992, Transferrin receptor specific antibody-neuropharmaceutical agent conjugates; Phillip Friden, 424/179.1, 85.2, 94.3, 152.1, 178.1, 181.1; 435/188; 530/302, 311, 351, 370, 388.22, 391.1, 391.3, 391.5, 391.7, 391.9, 399 [IMAGE AVAILABLE]

21. 5,120,525, Jun. 9, 1992, Radiolabeled antibody cytotoxic therapy of cancer; Milton D. Goldenberg, 424/1.41, 1.53, 85.2, 178.1 [IMAGE AVAILABLE]

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=> t 18, 22, 23 ti clm

US PAT NO: 5,332,567 [IMAGE AVAILABLE] L4: 18 of 24
TITLE: Detection and treatment of infections with immunoconjugates

CLAIMS:

CLMS(1)

What is claimed is:

1. A method of targeting a polyspecific diagnostic agent to a focus of infection, which comprises parenterally injecting a patient infected with a pathogen with an effective amount of a polyspecific diagnostic **antibody** **conjugate** comprising an immunoreactive composite of a plurality of chemically linked **antibodies** or **antibody** fragments which specifically bind to a plurality of epitopes on a single species of pathogen or an antigen shed by said pathogen or resulting from the fragmentation or destruction of said pathogen, wherein said conjugate further comprises at least one diagnostic agent.

CLMS(2)

2. The method of claim 1, wherein said agent is a diagnostic agent selected from the group consisting of a radioisotope and a magnetic resonance image enhancing agent.

CLMS(3)

3. The method of claim 1, wherein said **antibody** **conjugate** specifically binds to an accessible epitope of said pathogen or said antigen which is not saturated or blocked by the patient's native **antibodies**.

CLMS(4)

4. The method of claim 1, wherein said pathogen is a virus.

CLMS(5)

5. The method of claim 4, wherein said virus is an RNA virus.

CLMS(6)

6. The method of claim 4, wherein said virus is a DNA virus.

CLMS(7)

7. The method of claim 4, wherein said virus is selected from the group consisting of human immunodeficiency virus (HIV), herpes virus, cytomegalovirus, rabies virus, influenza virus, hepatitis B virus, Sendai virus, feline leukemia virus, Reo virus, polio virus, human serum parvo-like virus, simian virus 40, respiratory syncytial virus, mouse mammary tumor virus, Varicella-Zoster virus, Dengue virus, rubella virus, measles virus, adenovirus, human T-cell leukemia viruses, Epstein-Barr virus, murine leukemia virus, mumps virus, vesicular stomatitis virus, Sindbis virus, lymphocytic choriomeningitis virus, wart virus and blue tongue virus.

CLMS(8)

8. The method of claim 1, wherein said pathogen is a bacterium.

CLMS(9)

9. The method of claim 8, wherein said bacterium is selected from the group consisting of Streptococcus agalactiae, Legionella pneumophilia, Streptococcus pyogenes, Escherichia coli, Neisseria gonorrhoeae, Neisseria meningitidis, Pneumococcus, Hemophilis influenzae B, Treponema pallidum, Lyme disease spirochetes, Pseudomonas aeruginosa, Mycobacterium leprae, Brucella abortus, Mycobacterium tuberculosis and Tetanus toxin.

CLMS(10)

10. The method of claim 1, wherein said pathogen is a protozoan.

CLMS(11)

11. The method of claim 10, wherein said protozoan is selected from the group consisting of Plasmodium falciparum, Plasmodium vivax, Toxoplasma gondii, Trypanosoma rangeli, Trypanosoma cruzi, Trypanosoma rhodesiensei, Trypanosoma brucei, Schistosoma mansoni, Schistosoma japanicum, Babesia bovis, Elmeria tenella, Onchocerca volvulus, Leighmania tropica, Trichinella spiralis, Onchocerca volvulus, Theileria parva, Taenia hydatigena, Taenia ovis, Taenis sagenata, Echinococcus granulosus and Mesocestoides corti.

CLMS(12)

12. The method of claim 1, wherein pathogen is a helminth.

CLMS(13)

13. The method of claim 1, wherein said pathogen is mycoplasma.

CLMS(14)

14. The method of claim 13, wherein said mycoplasma is selected from the group consisting of Mycoplasma arthritidis, M. hyorhinis, M. **orale**, M. arginini, Acholeplasma laidlawii, M. salivarium and M. pneumoniae.

CLMS(15)

15. The method of claim 1, which further comprises administering to said patient, at a time after **administration** of said conjugate sufficient to optimize uptake of said conjugate at the site of said infection, an amount of a second **antibody** that specifically binds to said conjugate sufficient to reduce the amount of said conjugate in circulation by

10-85% within 2-72 hours.

CLMS(16)

16. The method of claim 1, wherein said polyspecific **antibody** **conjugate** comprises chemically linked **antibody** or **antibody** fragment components of an antiserum.

CLMS(17)

17. The method of claim 16, wherein said antiserum is affinity purified by removal of **antibodies** which bind to said antigen circulating at a significant level in the patient's bloodstream.

CLMS(18)

18. The method of claim 16, wherein said antiserum is affinity purified by contact with bound pathogen or bound antigen, and subsequent recovery of antiserum enriched in **antibodies** that bind to said pathogen or said antigen.

CLMS(19)

19. The method of claim 1, wherein said polyspecific **antibody** **conjugate** comprises chemically linked monoclonal **antibodies** or fragments thereof.

CLMS(20)

20. A polyspecific diagnostic **antibody** **conjugate** for targeting a focus of infection, comprising an immunoreactive composite of a plurality of chemically linked **antibodies** or **antibody** fragments which specifically bind to a plurality of epitopes on a single species of pathogen or an antigen shed by said pathogen or resulting from the fragmentation or destruction of said pathogen, wherein said conjugate further comprises at least one diagnostic agent.

CLMS(21)

21. The conjugate of claim 20, wherein said chemically linked **antibodies** or **antibody** fragments are components of an antiserum.

CLMS(22)

22. The conjugate of claim 21, wherein said antiserum is affinity purified by removal of **antibodies** which bind to said antigen circulating at a significant level in the patient's bloodstream.

CLMS(23)

23. The conjugate of claim 21, wherein said antiserum is affinity purified by contact with bound pathogen or bound antigen, and subsequent recovery of antiserum enriched in **antibodies** that bind to said pathogen or said antigen.

CLMS(24)

24. The conjugate of claim 20, wherein said polyspecific **antibody** **conjugate** comprises chemically linked monoclonal **antibodies** or fragments thereof.

CLMS(25)

25. A kit for use in preparing a sterile injectable preparation for targeting a focus of infection in a human patient, comprising in suitable containers, the polyspecific **antibody** **conjugate** of claim 20 and a pharmacologically acceptable sterile injection vehicle.

CLMS(26)

26. The kit of claim 25, wherein said chemically linked **antibodies** or **antibody** fragments are components of an antiserum.

CLMS(27)

27. The kit of claim 26, wherein said antiserum is affinity purified by removal of **antibodies** which bind to said antigen circulating at a significant level in the patient's bloodstream.

CLMS(28)

28. The kit of claim 26, wherein said antiserum is affinity purified by contact with bound pathogen or bound antigen, and subsequent recovery of antiserum enriched in **antibodies** that bind to said pathogen or said antigen.

CLMS(29)

29. The kid of claim 25, wherein said polyspecific **antibody** **conjugate** comprises chemically linked monoclonal **antibodies** or fragments thereof.

US PAT NO: 4,975,278 [IMAGE AVAILABLE] L4: 22 of 24
TITLE: Antibody-enzyme conjugates in combination with prodrugs for the delivery of cytotoxic agents to tumor cells

CLAIMS:

CLMS(1)

We claim:

1. A method for the **delivery** of cytotoxic agents to tumor cells comprising: the **administration** of an effective amount of at least one **antibody**-enzyme conjugate comprising an **antibody** reactive with an antigen on the surface of said tumor cells conjugated to an enzyme which converts at least one prodrug, that is weakly cytotoxic to tumor cells compared to its corresponding parent drug, into the more cytotoxic parent drug, and the **administration** of an effective amount of said prodrug.

CLMS(2)

2. The method of claim 1, wherein the **antibody** is selected from the group consisting of polyclonal, monoclonal or chimeric **antibodies**.

CLMS(3)

3. The method of claim 1, wherein the **antibody** is selected from the group consisting of monoclonal **antibodies** L6, 96.5 and 1F5.

CLMS(4)

4. The method of claim 1, wherein the enzyme is selected from the group consisting of alkaline phosphatases, penicillin amidases, arylsulfatases, cytosine deaminases, proteases, D-alanyl carboxypeptidases, carbohydrate-cleaving enzymes and .beta.-lactamases.

CLMS(5)

5. The method of claim 1, wherein the enzyme is alkaline phosphatase.

CLMS(6)

6. The method of claim 1, wherein the enzyme is a penicillin V amidase.

CLMS(7)

7. The method of claim 1, wherein the enzyme is cytosine deaminase.

CLMS(8)

8. The method of claim 1, wherein the parent drug is selected from the group consisting of etoposide, teniposide, adriamycin, daunomycin, carminomycin, aminopterin, dactinomycin, mitomycins, cis-platinum and cis-platinum analogues, bleomycins, esperamicins, 5-fluorouracil, melphalan and other nitrogen mustards.

CLMS(9)

9. The method of claim 1, wherein the parent drug is etoposide.

CLMS(10)

10. The method of claim 1, wherein the parent drug is a mitomycin.

CLMS(11)

11. The method of claim 1, wherein the parent drug is adriamycin.

CLMS(12)

12. The method of claim 1, wherein the parent drug is 5-fluorouracil.

CLMS(13)

13. The method of claim 1, wherein the prodrug is selected from the group consisting of phosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, glycosylated prodrugs, .beta.-lactam-containing prodrugs, D-amino acid-modified prodrugs, phenoxyacetamide-containing prodrugs or substituted-phenoxyacetamide-containing prodrugs, and phenylacetamide-containing prodrugs or substituted-phenylacetamide-containing prodrugs.

CLMS(14)

14. The method of claim 1, wherein the prodrug is selected from the group consisting of etoposide phosphates, etoposide thiophosphates, etoposide sulfates, teniposide phosphates, teniposide thiophosphates, teniposide sulfates, adriamycin phosphates, adriamycin sulfates, N.sup.7 -C.sub.1-8 alkyl mitomycin phosphates and N.sup.7 -C.sub.1-8 alkyl mitomycin sulfates.

CLMS(15)

15. The method of claim 1, wherein the prodrug is etoposide-4'-phosphate or a pharmaceutically acceptable salt thereof.

CLMS(16)

16. The method of claim 1, wherein the prodrug is 7-(2'-aminoethylphosphate)mitomycin or a pharmaceutically acceptable salt thereof.

CLMS(17)

17. The method of claim 1, wherein the prodrug is selected from the group consisting of N-(p-hydroxyphenoxyacetyl) adriamycin, N-(phenoxyacetyl)adriamycin, N-(p-hydroxyphenylacetyl)adriamycin and N-(phenylacetyl)adriamycin.

CLMS(18)

18. The method of claim 1, wherein the prodrug is selected from the group consisting of 5-fluorouridine monophosphate and 5-fluorocytosine.

CLMS(19)

19. The method of claim 1, wherein the **antibody**-enzyme conjugate is L6-AP.

CLMS(20)

20. The method of claim 1, wherein the **antibody**-enzyme conjugate is 96.5-AP.

CLMS(21)

21. The method of claim 1, wherein the **antibody**-enzyme conjugate is 1F5-AP.

CLMS(22)

22. The method of claim 1, wherein the **antibody**-enzyme conjugate is L6-PVA.

CLMS(23)

23. The method of claim 1, wherein the **antibody**-enzyme conjugate is 1F5-PVA.

CLMS(24)

24. The method of claim 1, wherein the **antibody**-enzyme conjugate is L6-CD.

CLMS(25)

25. The method of claim 1, wherein the **antibody**-enzyme conjugate is 1F5-CD.

CLMS(26)

26. The method of claim 1, wherein the **antibody**-enzyme conjugate is L6-AP and the prodrug is etoposide-4'-phosphate, N.sup.7 -C.sub.1-8 alkyl mitomycin phosphate or pharmaceutically acceptable salts thereof.

CLMS(27)

27. The method of claim 1, wherein the **antibody**-enzyme conjugate is L6-PVA and the prodrug is selected from the group consisting of N-(p-hydroxyphenoxyacetyl)adriamycin and N-(phenoxyacetyl)adriamycin.

CLMS(28)

28. The method of claim 1 wherein the **antibody**-enzyme conjugate is L6-CD and the prodrug is 5-fluorocytosine.

CLMS(29)

29. The method of claim 1, wherein the tumor cells are of an origin selected from the group consisting of carcinomas, melanomas, lymphomas, and bone and soft tissue sarcomas.

CLMS(30)

30. A method for the **delivery** of a combination of cytotoxic agents to tumor cells comprising: the **administration** of an effective amount of an **antibody**-enzyme conjugate comprising an **antibody** reactive with an antigen on the surface of said tumor cells conjugated to an enzyme which converts more than one prodrug, each of which is weakly cytotoxic to tumor cells compared to its corresponding parent drug, into the more cytotoxic parent drug, and the **administration** of an effective amount of more than one of said prodrugs.

CLMS(31)

31. The method of claim 1, wherein the enzyme is selected from the group consisting of alkaline phosphatases, penicillin amidases, arylsulfatases, cytosine deaminases, proteases, D-alanyl carboxypeptidases, carbohydrate-cleaving enzymes and .beta.-lactamases.

CLMS(32)

32. The method of claim 31, wherein the enzyme is alkaline phosphatase.

CLMS(33)

33. The method of claim 30, wherein the parent drug is selected from the group consisting of etoposide, teniposide, adriamycin, daunomycin, carminomycin, aminopterin, dactinomycin, mitomycins, cis-platinum and cis-platinum analogues, bleomycins, esperamicins, 5-fluorouracil, melphalan and other nitrogen mustards.

CLMS(34)

34. The method of claim 30, wherein the prodrugs are selected from the group consisting of phosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, glycosylated prodrugs, .beta.-lactam-containing prodrugs, D-amino acid-modified prodrugs, phenoxyacetamide-containing prodrugs or substituted-phenoxyacetamide-containing prodrugs, and phenylacetamide-containing prodrugs or substituted-phenylacetamide-containing prodrugs.

CLMS(35)

35. The method of claim 30, wherein the prodrugs are selected from the group consisting of etoposide phosphates, etoposide thiophosphates, etoposide sulfates, teniposide phosphates, teniposide thiophosphates, teniposide sulfates, adriamycin phosphate, adriamycin sulfates, N-phenoxyacetyl derivatives of adriamycin, N-phenylacetyl derivatives of adriamycin, N.sup.7 -C.sub.1-8 alkyl mitomycin phosphates and N.sup.7 -C.sub.1-8 alkyl mitomycin sulfates.

CLMS(36)

36. The method of claim 30, wherein one of the prodrugs is 5-fluorocytosine or 5-fluorouridine monophosphate.

CLMS(37)

37. The method of claim 30, wherein the prodrugs are etoposide-4'-phosphate, N.sup.7 -C.sub.1-8 alkyl mitomycin phosphate or pharmaceutically acceptable salts thereof.

CLMS(38)

38. The method of claim 30, wherein the **antibody**-enzyme conjugate is selected from the group consisting of L6-AP, 96.5-AP, and 1F5-AP.

CLMS(39)

39. The method of claim 30, wherein the **antibody**-enzyme conjugate is L6-AP and the prodrugs are etoposide-4'-phosphate and N.sup.7 -C.sub.1-8 alkyl mitomycin phosphate or pharmaceutically acceptable salts thereof.

CLMS(40)

40. A method for the **delivery** of a combination of cytotoxic agents to tumor cells comprising: the **administration** of an effective amount of more than one **antibody**-enzyme conjugate, wherein the **antibody** of each conjugate is reactive with the same or a different antigen located on the surface of said tumor cells and the enzyme of each conjugate is the same or different and which converts at least one prodrug, that is weakly cytotoxic to tumor cells compared to its corresponding parent drug, into the more cytotoxic parent drug, and the **administration** of an effectiVe amount of said prodrug or prodrugs.

CLMS(41)

41. The **antibody**-enzyme conjugate, L6-AP.

CLMS(42)

42. The **antibody**-enzyme conjugate, 96.5-AP.

CLMS(43)

43. The **antibody**-enzyme conjugate, 1F5-AP.

CLMS(44)

44. The **antibody**-enzyme conjugate, L6-PVA.

CLMS(45)

45. The **antibody**-enzyme conjugate, 1F5-PVA.

CLMS(46)

46. The **antibody**-enzyme conjugate, L6-CD.

CLMS(47)

47. The **antibody**-enzyme conjugate, 1F5-CD.

CLMS(48)

48. A compound having the formula: ##STR3## wherein: R.sup.1 is H, and

R.sup.3 is OH or OCH.sub.3 ; or
R.sup.1 is OH and R.sup.3 is OCH.sub.3 ; and
R.sup.2 is H or OH.

CLMS(49)

49. A compound having the formula: ##STR4## wherein: R.sup.1 is H, and R.sup.3 is OH or OCH.sub.3 ; or
R.sup.1 is OH and R.sup.3 is OCH.sub.3 ; and
R.sup.2 is H or OH.

CLMS(50)

50. N-(p-hydroxyphenoxyacetyl)adriamycin.

CLMS(51)

51. N-(phenoxyacetyl)adriamycin.

CLMS(52)

52. A pharmaceutically acceptable composition useful in the treatment of tumors which comprises a pharmaceutically effective amount of at least one **antibody**-enzyme conjugate according to claim 1.

CLMS(53)

53. A combination of at least one **antibody**-enzyme conjugate according to claim 1 and at least one prodrug that is weakly cytotoxic to tumor cells compared to its corresponding parent drug.

CLMS(54)

54. The combination of claim 53, wherein the **antibody**-enzyme conjugate is selected from the group consisting of L6-AP, L6-PVA and L6-CD.

CLMS(55)

55. The combination of claim 53, wherein the prodrug is selected from the group consisting of phosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, glycosylated prodrugs, .beta.-lactam-containing prodrugs, D-amino acid-modified prodrugs, phenoxyacetamide-containing prodrugs or substituted-phenoxyacetamide-containing prodrugs, and phenylacetamide-containing prodrugs or substituted-phenylacetamide-containing prodrugs.

CLMS(56)

56. The combination of claim 53, wherein the prodrug is selected from the group consisting of etoposide phosphates, etoposide thiophosphates, etoposide sulfates, teniposide phosphates, teniposide thiophosphates, teniposide sulfates, adriamycin phosphates, adriamycin sulfates, N-phenoxyacetyl derivatives of adriamycin, N-phenylacetyl derivatives of adriamycin, mitomycin phosphates, mitomycin sulfates, 5-fluorouridine monophosphate and 5-fluorocytosine.

CLMS(57)

57. The combination of claim 53, wherein the **antibody**-enzyme conjugate is L6-AP and the prodrug is etoposide-4'-phosphate, N.sup.7 -C.sub.1-8 alkyl mitomycin phosphate or pharmaceutically acceptable salts thereof.

CLMS(58)

58. A method for treating mammalian tumors comprising the step of administering to a mammal a pharmaceutically effective amount of at least one **antibody**-anzyme conjugate according to claim 1 and a pharmaceutically effective amount of at least one prodrug according to claim 1.

CLMS(59)

59. The method of claim 58, wherein the prodrug is selected from the group consisting of phosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, glycosylated prodrugs, .beta.-lactam-containing prodrugs, D-amino acid-modified prodrugs, phenoxyacetamide-containing prodrugs or substituted-phenoxyacetamide-containing prodrugs, and phenylacetamide-containing prodrugs or substituted-phenylacetamide-containing prodrugs.

CLMS(60)

60. The method of claim 58, wherein the prodrug is selected from the group consisting of 5-fluorouridine monophosphate and 5-fluorocytosine.

CLMS(61)

61. The method of claim 58, wherein the **antibody**-enzyme conjugate is L6-AP and the prodrug is etoposide-4'-phosphate, N.sup.7 -C.sub.1-8 alkyl mitomycin phosphate or pharmaceutically acceptable salts thereof.

CLMS(62)

62. A method for the **delivery** of cytotoxic agents to tumor cells comprising: the **administration** of an effective amount of at least one fusion protein comprising at least the antigen binding region of an **antibody** reactive with a tumor-associated antigen linked to at least a functionally active portion of an enzyme which converts at least one weakly cytotoxic prodrug into its more cytotoxic parent drug, and the **administration** of an effective amount of said prodrug.

CLMS(63)

63. The method of claim 62, wherein the **antibody** is selected from the group consisting of monoclonal **antibodies** L6, 96.5 and 1F5.

CLMS(64)

64. The method of claim 62, wherein the enzyme is selected from the group consisting of alkaline phosphatases, penicillin amidases, aryl sulfatases, cytosine deaminases, proteases, D-alanyl carboxypeptidases, carbohydrate-cleaving enzymes and .beta.-lactamases.

US PAT NO: 4,952,394 [IMAGE AVAILABLE] L4: 23 of 24
TITLE: Drug-monoclonal **antibody** **conjugates**

CLAIMS:

CLMS(1)

What is claimed is:

1. An anti-tumor drug-Monoclonal **antibody** **conjugate** having the general structural formula: ##STR3## wherein: D is an anti-tumor drug

moiety having pendant to the backbone thereof a chemically reactive functional group, by means of which the drug backbone is bonded to the disulfide benzyloxycarbonyl group, derived from the group consisting of a primary amino group represented by the formula R.sup.1 NH--, a secondary amino group represented by the formula R.sup.1 R.sup.2 N--, and an alcohol group represented by the formula R.sup.1 O--;

R.sup.1, when R.sup.1 and R.sup.2 are independent, is the backbone of said drug moiety when D is derived from the group consisting of a primary amino group, a secondary amino group, and an alcohol group;

R.sup.2, when R.sup.1 and R.sup.2 are independent, is selected from unsubstituted and substituted and branched and straight-chain alkyl groups having 1-10 carbon atoms wherein the substitutent is selected from 1 to 3 alkoxy groups having 1 to 3 carbon atoms and 1 to 3 halo groups; unsubstituted and substituted phenyl wherein the substituent is selected from 1 to 3 alkyl groups having 1 to 3 carbon atoms, 1 to 3 alkoxy groups having 1 to 3 carbon atoms, and 1 to 3 halo groups; and unsubstituted and substituted phenalkyl wherein the phenyl moiety, when substituted, is substituted as defined above in the case of substituted phenyl and the alkyl moiety is a polyalkylene group having 1 to 3 carbon atoms;

R.sup.1 and R.sup.2, when taken together in a functional group derived from a secondary amine, represent the backbone of the drug moiety, D, having a divalent group chemically bonded to the nitrogen atom constituting said secondary amino group; and

R.sup.3 and R.sup.4, independently, are selected from H and unsubstituted and substituted, and branched and straight-chain alkyl groups having 1-10 carbon atoms wherein the substitutent is selected from 1 to 3 alkoxy groups having 1 to 3 carbon atoms and 1 to 3 halo groups; unsubstituted and substituted phenyl wherein the substituent is selected from 1 to 3 alkyl groups having 1 to 3 carbon atoms, 1 to 3 alkoxy groups having 1 to 3 carbon atoms, and 1 to 3 halo groups; and unsubstituted and substituted phenylalkyl wherein the phenyl moiety, when substituted, is substituted as defined above in the case of substituted phenyl and the alkyl moiety is a polyalkylene group having 1 to 3 carbon atoms;

m is an integer selected from 1 to 10; and

Ab represents a monoclonal **antibody** having a pendent amino group; and

the orientation of the group, ##STR4## on the phenyl ring of the benzylcarbamate moiety is selected from the ortho- and para-positions.

CLMS(2)

2. An anti-tumor drug-monoclonal **antibody** **conjugate** according to claim 1 wherein the drug moiety, D, is a member selected from the group consisting of primary amine-containing and secondary amine-containing drugs.

CLMS(3)

3. An anti-tumor drug-monoclonal **antibody** **conjugate** according to claim 2 wherein the drug moiety, D, is a member selected from mitomycin-C, mitomycin-A, daunomycin, adriamycin, aminoptecin, actinomycin, bleomycin, and derivatives thereof.

CLMS(4)

4. An anti-tumor drug-monoclonal **antibody** **conjugate** according to claim 1 wherein, the drug moiety, D, is an alcohol group-containing drug.

CLMS(5)

5. An anti-tumor drug-monoclonal **antibody** **conjugate** according to

claim 4 wherein the drug moiety, D, is etoposide.

CLMS(6)

6. A method for **delivering** to the site of tumor cells in a mammal having enhanced levels of endogenous reducing agents which reducing agents include at least one member of the group of NADH, NADPH and glutathione, an active anti-tumor drug having pendant to the backbone thereof a chemically reactive functional group selected from the group consisting of a primary amino group represented by the formula R.sup.1 NH--, a secondary amino group represented by the formula R.sup.1 R.sup.2 N--, and an alcohol group represented by the formula R.sup.1 O wherein R.sup.1 and R.sup.2 are as defined in claim 1 above, comprising the steps of:

(a) administering to a mammal an antitumor effective amount of anti-tumor drug-monoclonal **antibody** **conjugate** according to claim 1;

(b) contacting the anti-tumor drug-monoclonal **antibody** **conjugate** from step (a) with endogenous reducing conditions, and

(c) permitting the anti-tumor drug-monoclonal **antibody** **conjugate** to undergo reductive cleavage to release free drug from the conjugate.

=> antibod?/clm and tablets/clm

'ANTIBOD?' IS NOT A RECOGNIZED COMMAND

=> s antibod?/clm and tablet?/clm

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          8937 ANTIBOD?/CLM
          6345 TABLET?/CLM
L5          40 ANTIBOD?/CLM AND TABLET?/CLM
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=> t l5 1-20

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US PAT NO: 5,160,742 [IMAGE AVAILABLE] L5: 19 of 40
TITLE: System for delivering an active substance for sustained release

CLAIMS:

CLMS(1)

What is claimed is:

1. A system for delivery of an active substance for sustained release in the intestinal tract, comprising a particle having a core containing an active substance, said core being encapsulated by at least two layers of coating materials, one of said layers of a coating material consisting essentially of a prolamine and at least one material selected from the group consisting of plasticizers and hydrophobic substances and the other layer a coating material consisting essentially of an enteric compound and at least one material selected from the group consisting of plasticizers and anti-tackiness agents, such that said other layer is generally resistant to disintegration in human gastric juices but will disintegrate in human intestinal fluids.

CLMS(2)

2. A system for delivery of an active substance for sustained release in the intestinal tract according to claim 1 wherein the core is encapsulated by a first layer of a coating material, consisting essentially of a prolamine and at least one material selected from the group consisting of plasticizers and hydrophobic substances said first layer is encapsulated by an exterior layer of a coating material consisting essentially of an enteric compound and at least one material selected from the group consisting of plasticizers and anti-tackiness agents, such that said exterior layer is generally resistant to disintegration in human gastric juices but will disintegrate in human intestinal fluids.

CLMS(3)

3. A system for delivery of an active substance for sustained release in the intestinal tract according to claim 1 wherein the core is encapsulated by a first layer of a coating material consisting essentially of an enteric compound and at least one material selected from the group consisting of plasticizers and anti-tackiness agents, such that said first layer is generally resistant to disintegration in human gastric juices but will disintegrate in human intestinal fluids, and said first layer is encapsulated by an exterior layer of a coating material consisting essentially of a prolamine and at least one material selected from the group consisting of plasticizers and hydrophobic substances.

CLMS(4)

4. A system for delivery of an active substance for sustained release in the intestinal tract according to claim 1 wherein the core is encapsulated by a first layer comprising a coating material consisting essentially of a prolamine and at least one material selected from the group consisting of plasticizers and hydrophobic substances, said first layer is encapsulated by a second layer comprising a coating material consisting essentially of an enteric compound and at least one material selected from the group consisting of plasticizers and anti-tackiness agents, such that said second layer is generally resistant to disintegration in human gastric juices but will disintegrate in human intestinal fluids, and said second layer is encapsulated by an exterior layer comprising a coating material consisting essentially of a prolamine and at least one material selected from the group consisting of plasticizers and hydrophobic substances.

CLMS(5)

5. A system for delivery of an active substance for sustained release in the intestinal tract according to any one of claims 1 through 4 wherein the prolamine is zein.

CLMS(6)

6. A system for delivery of an active substance for sustained release in the intestinal tract according to any one of claims 1 through 4 wherein the enteric compound comprises at least one material selected from the group consisting of acids and esters of methacrylic copolymers.

CLMS(7)

7. A system for delivery of an active substance for sustained release in the intestinal tract according to claim 5 wherein the enteric compound comprises at least one material selected from the group consisting of acids and esters of methacrylic copolymers.

CLMS(8)

8. A system for delivery of an active substance for sustained release in the intestinal tract according to any one of claims 1 through 4 comprising a plurality of said particles where in the particles have a size of not greater than about 700 microns, and the system further comprises a liquid medium, said particles being disposed within said liquid medium.

CLMS(9)

9. A system for delivery of an active substance for release in the intestinal tract according to claim 8 wherein the liquid medium is an aqueous medium.

CLMS(10)

10. A system for delivery of an active substance for release in the intestinal tract according to claim 9 wherein the prolamine is zein and the enteric compound comprises at least one material selected from the group consisting of acids and esters of methacrylic copolymers.

CLMS(11)

11. A system for delivery of an active substance for release in the intestinal tract according to claim 10 wherein the active substance is a .beta.-lactam antibiotic.

CLMS(12)

12. A system for delivery of an active substance for release in the intestinal tract according to claims 1 through 4 wherein the active substance is selected from the group consisting of analgesics, antibiotics, antidepressants, antivirals, **antibodies**, immuno-modulators, oncolytics, immunogens, hormones, vaccines, enzymes, nutrients and dietary fiber.

CLMS(13)

13. A system for delivery of an active substance for release in the intestinal tract comprising a particle having a core containing an active substance, said core being encapsulated by a first layer of a coating material consisting essentially of an enteric compound in an amount of about 10% to 70% of the total weight of the core and at least one material selected from the group consisting of plasticizers and anti-tackiness agents, such that said first coating layer is generally resistant to disintegration in human gastric juices but will disintegrate in human intestinal fluids, and said first coating layer being encapsulated by an exterior layer of a coating material consisting essentially zein in the amount of about 20% to 100% by weight of the sum of the weights of the core and the first coating layer and at least one material selected from the group consisting of plasticizers and hydrophobic substances.

CLMS(14)

14. A system for delivery of an active substance for release in the intestinal tract according to claim 13 wherein the enteric compound comprises at least one material selected from the group consisting of acids and esters of methacrylic copolymers.

CLMS(15)

15. A system for delivery of an active substance for release in the intestinal tract according to claim 14 wherein the zein has an ash content of not greater than about 2% by weight.

CLMS(16)

16. A system for delivery of an active substance for release in the intestinal tract according to any one of claims 13 through 15 wherein the active substance is selected from the group consisting of analgesics, antibiotics, antidepressants, antivirals, **antibodies**, immuno-modulators, oncolytics, immunogens, hormones, vaccines, enzymes, nutrients and dietary fiber.

CLMS(17)

17. A system for delivery of an active substance for release in the intestinal tract according to any one of claims 13 through 15 wherein the active substance is a .beta.-lactam antibiotic.

CLMS(18)

18. A system for delivery of an active substance for release in the intestinal tract comprising a particle having a core containing an active substance, said core being encapsulated by a first layer of a coating material consisting essentially of zein in the amount of about 10% to 70% of the total weight of the core and at least one material selected from the group consisting of plasticizers and hydrophobic substances, and said

first coating layer being encapsulated by a second coating layer consisting essentially of an enteric compound in an amount of about 10% to 70% of the sum of the weights of the core and the first coating layer and at least one material selected from the group consisting of plasticizers and anti-tackiness agents, such that said second coating layer is generally resistant to disintegration in human gastric juices but will disintegrate in human intestinal fluids.

CLMS(19)

19. A system for delivery of an active substance for release in the intestinal tract according to claim 18 wherein the particle is in the form of a **tablet**.

CLMS(20)

20. A system for delivery of an active substance for release in the intestinal tract according to either of claims 18 or 19 wherein the active substance is selected from the group consisting of analgesics, antibiotics, antidepressants, antivirals, **antibodies**, immuno-modulators, oncolytics, immunogens, hormones, vaccines, enzymes, nutrients and dietary fiber.

CLMS(21)

21. A system for delivery of an active substance for release in the intestinal tract according to either of claims 18 or 19 wherein the active substance is a .beta.-lactam antibiotic.

CLMS(22)

22. A system for delivery of an active substance for release in the intestinal tract comprising a particle having a core containing an active substance, said core being encapsulated by a first layer of a coating material consisting essentially of zein in an amount of about 10% to 70% of the total weight of the core and at least one material selected from the group consisting of plasticizers and hydrophobic substances, said first coating layer being encapsulated by a second coating layer consisting essentially of an enteric compound in the amount of about 5% to 70% of the sum of the weights of the core and first coating layer and at least one material selected from the group consisting of plasticizers and anti-tackiness agents, such that said layer is generally resistant to disintegration in human gastric juices but will disintegrate in human intestinal fluids, and said second coating layer being encapsulated by an exterior coating layer of a coating material consisting essentially of zein in an amount of about 20% to 70% of the sum of the weights of the core and the first two coating layers and at least one material selected from the group consisting of plasticizers and hydrophobic substances.

CLMS(23)

23. A system for delivery of an active substance for release in the intestinal tract according to claim 22 wherein the zein has an ash content of not greater than about 2% by weight.

CLMS(24)

24. A system for delivery of an active substance for release in the intestinal tract according to claim 22 wherein the enteric compound comprises at least one material selected from the group consisting of acids and esters of methacrylic copolymers.

CLMS(25)

25. A system for delivery of an active substance for release in the intestinal tract according to claim 23 wherein the enteric compound comprises at least one material selected from the group consisting of acids and esters of methacrylic copolymers.

CLMS(26)

26. A system for delivery of an active substance for release in the intestinal tract according to any one of claims 22 through 25 wherein the active substance is selected from the group consisting of analgesics, antibiotics, antidepressants, antivirals, **antibodies**, immuno-modulators, oncolytics, immunogens, hormones, vaccines, enzymes, nutrients and dietary fiber.

CLMS(27)

27. A system for delivery of an active substance for release in the intestinal tract according to any one of claims 22 through 25 wherein the active substance is a .beta.-lactam antibiotic.

CLMS(28)

28. A system for delivery of an active substance for release in the intestinal tract comprising a liquid medium having a plurality of particles disposed therein, said particles comprising a core containing an active substance, said core being encapsulated by at least two layers of coating materials, one of said layers comprising a coating material, consisting essentially of zein and least one material selected from the group consisting of plasticizers and hydrophobic substances and the other layer comprising a coating material consisting essentially of an enteric compound and at least one material selected from the group consisting of plasticizers and anti-tackiness agents, such that said other layer is generally resistant to disintegration in human gastric juices but will disintegrate in human intestinal fluids, said particles having sizes of not greater than about 700 microns.

CLMS(29)

29. A system for delivery of an active substance for release in the intestinal tract according to claim 28 wherein said particles have a structure such that the core is encapsulated by a first layer comprising a coating material, consisting essentially of zein and at least one material selected from the group consisting of plasticizers and hydrophobic substances and said first layer is encapsulated by an exterior layer comprising a coating material consisting essentially of an enteric compound and at least one material selected from the group consisting of plasticizers and anti-tackiness agents, such that said second layer is generally resistant to disintegration in human gastric juices but will disintegrate in human intestinal fluids.

CLMS(30)

30. A system for delivery of an active substance for release in the intestinal tract according to claim 28 wherein said particles have a structure such that the core is encapsulated by a first layer comprising a coating material, consisting essentially of an enteric compound and at least one material selected from the group consisting of plasticizers and anti-tackiness agents, such that said first layer is generally resistant to disintegration in human gastric juices but will disintegrate in human intestinal fluids, and said first layer is encapsulated by an exterior layer comprising a coating material consisting essentially of zein and at least one material selected from the group consisting of plasticizers and

hydrophobic substances

CLMS(31)

31. A system for delivery of an active substance for release in the intestinal tract according to claim 28 wherein said particles have a structure such that the core is encapsulated by a first layer comprising a coating material, consisting essentially of zein and at least one material selected from the group consisting of plasticizers and hydrophobic substances and said first layer is encapsulated by a second layer comprising a coating material, consisting essentially of an enteric compound and at least one material selected from the group consisting of plasticizers and anti-tackiness agents, such that said second layer is generally resistant to disintegration in human gastric juices but will disintegrate in human intestinal fluids, and said second layer is encapsulated by an exterior layer comprising a coating material consisting essentially of zein and at least one material selected from the group consisting of plasticizers and hydrophobic substances.

CLMS(32)

32. A system for delivery of an active substance for release in the intestinal tract according to claim 28 wherein the zein has an ash content of not greater than about 2% by weight, and the enteric compound comprises at least one material selected from the group consisting of acids and esters of methacrylic copolymers.

CLMS(33)

33. A system for delivery of an active substance for release in the intestinal tract according to claim 29 wherein the zein has an ash content of not greater than about 2% by weight, and the enteric compound comprises at least one material selected from the group consisting of acids and esters of methacrylic copolymers.

CLMS(34)

34. A system for delivery of an active substance for release in the intestinal tract according to claim 30 wherein the zein has an ash content of not greater than about 2% by weight and the enteric compound comprises at least one material selected from the group consisting of acids and esters of methacrylic copolymers.

CLMS(35)

35. A system for delivery of an active substance for release in the intestinal tract according to claim 31 wherein the zein has an ash content of not greater than about 2% by weight, and the enteric compound comprises at least one material selected from the group consisting of acids and esters of methacrylic copolymers.

CLMS(36)

36. A system for delivery of an active substance for release in the intestinal tract according to any one of claims 28 through 35 wherein the liquid medium is an aqueous medium.

CLMS(37)

37. A system for delivery of an active substance for release in the intestinal tract according to any one of claims 28 through 35 wherein the active substance is selected from the group consisting of analgesics, antibiotics, antidepressants, antivirals, **antibodies**,

immuno-modulators, oncostics, immunogens, hormones, vaccines, enzymes, nutrients and dietary fiber.

CLMS(38)

38. A system for delivery of an active substance for release in the intestinal tract according to either of claims 28 or 35 wherein the active substance is a .beta.-lactam antibiotic.

CLMS(39)

39. A system for delivery of an active substance for release in the intestinal tract according to claim 36 wherein the active substance is an antibiotic.

CLMS(40)

40. A system for delivery of an active substance for release in the intestinal tract according to claim 36 wherein the active substance is a .beta.-lactam antibiotic.

US PAT NO: 4,689,221 [IMAGE AVAILABLE] L5: 27 of 40
TITLE: Oral composition containing antibodies to Bacteroides gingivalis

CLAIMS:

CLMS(1)

What is claimed is:

1. A dentifrice composition suitable for application to the mouth, comprising:
an effective amount to suppress the intraoral colonization of Bacteroides gingivalis of an **antibody** obtained by immunizing a mammalian animal with an immunologically effective amount of at least one antigen selected from the group consisting of Bacteroides gingivalis, a pilus fraction of Bacteroides gingivalis and a capsule fraction of Bacteroides gingivalis;
5 to 95% by weight of an abrasive; and
an orally acceptable carrier.

CLMS(2)

2. The composition of claim 1, wherein said **antibody** is present in an amount of 0.002 to 10% by weight of the composition.

CLMS(3)

3. The composition of claim 1, wherein said **antibody** is present in an amount of 0.002 to 5% by weight of the composition.

CLMS(4)

4. The composition of claim 1, which has a pH of from 5 to 10.

CLMS(5)

5. A method for treating periodontal disease in mammals caused by Bacteroides gingivalis which comprises applying to the mouth of a mammal an effective amount of the composition comprising:
an effective amount to suppress the intraoral colonization of Bacteroides gingivalis of an **antibody** obtained by immunizing a

mammalian animal with an immunologically effective amount of at least one antigen selected from the group consisting of Bacteroides gingivalis, a pilus fraction of Bacteroides gingivalis and a capsule fraction of Bacteroides gingivalis; and
an orally acceptable carrier to suppress the growth of Bacteroides gingivalis.

CLMS(6)

6. The method of claim 5, wherein the teeth of said mammal are brushed with said composition.

CLMS(7)

7. The method of claim 5, wherein said **antibody** in said composition is administered in an amount of 0.0001 to 50 g/kg/day based on the weight of said mammal.

CLMS(8)

8. The composition of claim 5, wherein said antigen is a whole cell antigen of Bacteroides gingivalis.

CLMS(9)

9. The composition of claim 1, wherein said antigen is the capsule fraction of Bacteroides gingivalis.

CLMS(10)

10. The composition of claim 1, wherein said antigen is the pilus fraction of Bacteroides gingivalis.

CLMS(11)

11. An oral composition suitable for application to the mouth, comprising:
an effective amount to suppress the intraoral colonization of Bacteroides gingivalis of an **antibody** obtained by immunizing a mammal selected from the group consisting of a rabbit, goat, sheet, horse and cow with at least one antigen selected from the group consisting of Bacteroides gingivalis, its pilus and capsule fractions wherein said effective amount is 0.0002 to 10% by weight of the composition;
5 to 95% by weight of the composition of an abrasive; and
an orally acceptable carrier.

CLMS(12)

12. The composition of claim 11, wherein said **antibody** is separated and purified from antiserum or milk from a mammal which has been immunized with said antigen.

CLMS(13)

13. The composition of claim 11, wherein antiserum or milk obtained from a mammal which has been immunized with said antigen is added to the composition.

CLMS(14)

14. The composition of claim 11, wherein said **antibody** is present in an amount of 0.002 to 5% by weight of the composition.

CLMS(15)

15. The composition of claim 11, wherein said **antibody** is obtained by subcutaneously injecting said mammal with an antigen of Bacteroides gingivalis, thereafter intraveneously injecting said mammal with said antigen of Bacteroides gingivalis, collecting antiserum from the thus immunized mammal, salting-out the **antibody** from the antiserum and dialyzing said **antibody** to obtain a purified **antibody**.

CLMS(16)

16. A method for treating periodontal disease in mammals caused by Bacteroides gingivalis which comprises applying to the mouth of a mammal an effective amount of a composition comprising:
an effective amount to suppress the intraoral colonization of Bacteroides gingivalis of an **antibody** obtained by immunizing a mammal selected from the group consisting of a rabbit, goat, sheep, horse and cow with at least one antigen selected from the group consisting of Bacteroides gingivalis, its pilus and capsule fractions; and an orally acceptable carrier to suppress the growth of Bacteroides gingivalis.

CLMS(17)

17. The method of claim 16, wherein the teeth of said mammal are brushed with said composition.

CLMS(18)

18. The method of claim 16, wherein said **antibody** in said composition is administered in an amount of 0.0001 to 50 g/kg/day based on the weight of said mammal.

CLMS(19)

19. An oral composition suitable for application to the mouth, comprising:
an effective amount to suppress the intraoral colonization of Bacteroides gingivalis of a purified serum or milk **antibody** obtained by immunizing a mammalian animal with an immunologically effective amount of at least one antigen selected from the group consisting of Bacteroides gingivalis, a pilus fraction of Bacteroides gingivalis and a capsule fraction of Bacteroides gingivalis; and an orally acceptable carrier, said oral composition being in the form of a dentifrice, a liquid refrigerant, a solid refrigerant, a dental paste, a gingival massage cream, a gargle **tablet** or a dairy product.

CLMS(20)

20. The composition of claim 19, in the form of a dentifrice.

CLMS(21)

21. The composition of claim 19, in the form of a dental paste.

CLMS(22)

22. The composition of claim 19, in the form of a gingival massage cream.

CLMS(23)

23. The composition of claim 19, wherein said **antibody** is obtained by immunizing said mammal, collecting antiserum from said mammal, purifying said **antibody** in said serum and adding said purified **antibody** to said oral composition.

CLMS(24)

24. The composition of claim 19, wherein said **antibody** is obtained by immunizing said mammal with a pilus fraction of Bacteroides gingivalis.

CLMS(25)

25. The composition of claim 19, wherein said **antibody** is obtained by immunizing said mammal with a capsule fraction of Bacteroides gingivalis.

CLMS(26)

26. An oral composition suitable for application to the mouth, comprising:
an effective amount to suppress the intraoral colonization of Bacteroides gingivalis of an anti-pilus fraction of Bacteroides gingivalis **antibody** or an anti-capsule fraction of Bacteroides gingivalis **antibody**; and
an orally acceptable carrier.

CLMS(27)

27. The composition of claim 26, wherein said **antibody** is an anti-pilus of Bacteroides gingivalis **antibody**.

CLMS(28)

28. The composition of claim 26, wherein said **antibody** is an anti-capsule fraction of Bacteroides gingivalis **antibody**.

CLMS(29)

29. The composition of claim 26, wherein said **antibody** is a serum **antibody**.

CLMS(30)

30. A method for treating periodontal disease in mammals caused by Bacteroides gingivalis which comprises applying to the mouth of a mammal an effective amount of the composition of claim 32.

CLMS(31)

31. The method of claim 30, wherein said composition is applied to the mouth by brushing buccal and lingual surfaces of molars.

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